

(1991). Health risk assessment of aerial application of Malathion-Bait, California Department of Health Services.

EXECUTIVE SUMMARY

The purpose of this document is to provide a comprehensive review of the toxicological literature on malathion, provide dose estimates associated with potential exposures during aerial malathion-bait application as conducted in California, assess public health risks from these exposures, and provide recommendations for further investigations that would reduce the uncertainties encountered in evaluating these risks. To accomplish this, the staff of the Department of Health Services (DHS) reviewed and analyzed information relating to the human health effects of malathion, its metabolites and impurities. Reviews of chemistry, metabolism, and toxicological and epidemiological data were conducted by over 30 DHS staff scientists and physicians. DHS staff relied heavily on on-line searches of bibliographic databases extended to their origins (ca. 1966). Unpublished documents and studies submitted in support of malathion registration were also reviewed. In total, nearly 2300 citations were evaluated and over 500 of these were specifically reviewed for this document. The risk assessment also uses environmental monitoring data provided by the California Department of Food and Agriculture (CDFA) and other agencies.

All technical sections of this document were presented by DHS staff and discussed at public meetings of the Malathion Public Health Effects Advisory Committee (MPHEAC). Members of MPHEAC also participated in subcommittees to evaluate selected issues in greater depth with assistance of DHS staff. The MPHEAC members reviewed the drafts of this document, provided advice and recommendations to DHS, and as a committee are in general agreement with the conclusions presented herein.

Malathion (S-(1,2-dicarbethoxyethyl) O,O-dimethyldithiophosphate) was introduced in 1950 by the American Cyanamid Company as a broad spectrum insecticide. The “commercial” or technical grade product varies from approximately 90 to 95% by weight and may contain approximately a dozen impurities formed during manufacture or storage. The most important impurities (in terms of concentrations) are isomalathion, malaoxon (also a minor metabolite), O,S,S-trimethylphosphorodithioate (OSS(O)), O,O,S-trimethylphosphorothioate (OOS(O)), O,O,S-trimethyl phosphorodithioate (OOS(S)), and diethyl fumarate.

Monitoring and environmental fate data on malathion and malaoxon following aerial bait application were used to estimate human exposure via three pathways: inhalation, ingestion, and dermal contact. Human exposures were considered to be of short-term duration (acute), months (subchronic) or years (chronic). Acute, subchronic, and chronic dose estimates were developed for each exposure pathway for both malathion and malaoxon based on actual or estimated averages and upper confidence limits of environmental concentrations.

A total of 25 exposure scenarios were developed and evaluated which included a broad range of exposure assumptions based on adult’s and children’s activities. Dose estimates for acute (one time) exposure to malathion by inhalation in the general growth retardation and weak associations with spontaneous abortion and stillbirths for certain exposure variables, but these

associations were not consistent or statistically significant. Malathion is not considered by DHS to be a reproductive or developmental toxicant. However, this determination is based in part on a lack of adequate study data and should be viewed as an interim conclusion until more definitive data are made available.

A number of studies were reviewed which investigated the adverse effects of malathion and its coproducts on the immune systems at both toxic and nontoxic dose levels. Contact sensitization was suggested in a human study but delayed hypersensitivity was not confirmed in animal studies. Acute doses of the malathion impurity OOS(O) have been reported to cause a variety of immunological effects in mice. Three epidemiological studies addressed immune function in pesticide workers, but multiple pesticide exposures were reported in all studies, and these results are not useful for risk characterization. Based on the review of the studies available on immunotoxicity of malathion and coproducts, DHS concludes that the database is not complete for this endpoint.

Evidence of the gene-damaging abilities of technical grade malathion is provided by results from several *in vivo* studies in which dermal or intraperitoneal administration to test animals produced significant chromosomal damage in cells located in the bone marrow. These results were not duplicated with purified (>99%) malathion. Pesticide applicators with exposures to technical grade malathion and other pesticides have higher levels of chromosomal damage. Because exposures to other clastogenic agents were not adequately controlled in these studies, the effects are of questionable relevance. Results from *in vitro* studies of technical grade malathion in cultured human, hamster, or buffalo cells indicated significant increases in chromosomal aberrations or sister-chromatid exchanges (SCEs). Increased in chromosomal aberrations in human lymphocytes or hamster ovary cells were reported in five studies reviewed in this document, and all studies which examined the effect of technical malathion or malaoxon on SCEs frequencies in human and hamster cell lines were positive. On the other hand, the majority of results from gene mutation assays were negative.

The human health implications of these studies are uncertain, but the association of mutagenic and carcinogenic effects if well known in experimental animals and many human cancers are now known to results from specific mutational events. Thus, the genotoxic potential of malathion and malaoxon provides some mechanistic support for a carcinogenic potential for these agents in experimental animals and humans and positive genotoxic responses should be considered adverse effects. Genotoxic effects, in turn, may be the result of the impurities found in technical grade malathion.

DHS staff and members of MPHEAC reviewed the available data and the reevaluations of the malathion/malaoxon cancer bioassays. DHS concludes that the available data do not provide evidence of a carcinogenic effect of malathion in either Osborne-Mendel or F344 rats, or in B6C3F1 mice. IN addition, DHS concludes that there is equivocal evidence of a carcinogenic effect for malaoxon in male and female F344 rats arising from the increased incidences of thyroid C-cell adenoma/carcinomas among dosed animals compared to the controls. Although a dose-related trend of tumor incidence was statistically significant in male and female rats, it was not seen at all in mice, and there was no effect induced at this cancer site by malathion (which is metabolized in part to malaoxon).

Determination of a chemical to be considered carcinogenic by DHS requires at least two positive studies. Therefore, due to the lack of adequate evidence of carcinogenicity, DHS does not classify malathion or malaoxon as a carcinogen and a cancer potency determination was not presented in this health risk assessment. The demonstrated potential for malathion (and malaoxon) to exhibit genetic toxicity in a variety of *in vitro* and *in vivo* assays suggests a possible mechanism of cancer causation (i.e., via gene damage). Many chemical mutagens have been found to be animal carcinogens. Additional chronic studies of malathion and malaoxon are needed to research the endocrine pathology and the mechanism of malathion and malaoxon genotoxicity.

A number of non-cancer toxicological endpoints were evaluated by DHS, including ocular effects, dermal and mucous membrane irritation, neurotoxicity, immunotoxicity, reproductive toxicity, developmental toxicity, genetic toxicity, and other effects. To evaluate the potential for non-cancer effects from exposure to malathion (and malaoxon) following aerial bait application, the threshold for toxicity was estimated and a reference exposure level (REL) was calculated for those endpoint for which an adequate database exists. An REL is a level at which no adverse health effects are anticipated. Therefore, health protection is achieved if the estimated or actual human dose of malathion is below the relevant REL(s). Exposures greater than the REL, however, are not necessarily hazardous, and do not absolutely result in significant health risks.

Because threshold doses are difficult to define experimentally or from epidemiological data, other exposure levels are used to approximate the threshold dose. Experimentally, these exposure levels are determined for a non-cancer endpoint as a no-observed-adverse-effect-level (NOAEL), a no-observed-effect-level (NOEL), a lowest-observed-adverse-effect level (LOAEL), or a lowest-observed-effect level (LOEL). The selection of a toxicological endpoint and the exposure levels associated with the observations of those endpoints is dependent on the availability and adequacy of the existing database. Uncertainty factors (usually factors of 10) were applied to account for inter-species variability, intra-species variability, intra-species variability, the absence of a no-observed-adverse-effect-level, experimental design and duration, and the adequacy of the database. By dividing estimated threshold doses by applicable uncertainty factors, RELs were obtained. The use of uncertainty factors provides a health-protective approach to risk assessment, and there is widespread agreement in the scientific community that this approach is likely to result in adequate margins of safety for the general population.

The lowest RELs determined for acute exposure were: dermal irritation, 2.8 mg/day (adult, topical dose); and blood AChE inhibition, 0.02 mg/kg-day for malathion, and 0.002 mg/kg-day for malaoxon. The lowest RELs determined for subchronic and chronic exposure were: blood AChE inhibition, 0.002 mg/kg-day for malathion, and 0.0002 mg/kg-day for malaoxon.

The potential acute, subchronic, or chronic doses of malathion exposure estimated in the risk assessment under several scenarios are, in general, below RELs developed to protect public health. Therefore, after a thorough review of the available literature and documentation on the toxicology of malathion and its coproducts, and after performing a health-conservative risk assessment, DHS concludes that following nighttime aerial applications of malathion-bait, as implemented by CDFA during the 1990 Medfly Eradication Program in southern California,

most individuals would not be expected to develop any adverse health effects. DHS also concludes that although the data are incomplete, there is insufficient evidence to classify malathion or malaoxon as a carcinogen, a teratogen, a reproductive toxicant, or to support causality for irreversible eye damage.

Under certain exposure scenarios, however, dose estimates were greater than the relevant RELs (developed for skin irritation and 20% inhibition of AChE activity) by more than 10-fold. These exposure scenarios include individuals eating vegetables grown in the backyard, and individuals spending a minimum of four hours each day outdoors wearing only shorts during or following malathion-bait application. Thus, there is little or no margin of safety for individuals that would receive malathion doses as estimated for certain exposure scenarios. Based on these results, DHS believes that a subpopulation of potentially sensitive individuals such as children, the aged, individuals with certain pre-existing diseases, and the homeless who receive upper-bound exposures (and in some cases average exposures) to malathion may be at risk of exhibiting some adverse health effects from

ld be considered when feasible. Washing of fruits and vegetables obtained from backyard (and supermarkets) is prudent public health practice in any case, and would remove much of the residues of malathion from aerial bait application. DHS made similar recommendation back in February, 1990, when it first became involved in the 1990 Medfly Eradication Program.

While individual actions can reduce health risks associated with malathion applications, DHS believes that there is a need for the development of additional information on specific biological endpoints, especially if aerial application in urban areas continues to be used as a treatment for Medfly eradication. These include studies on ACHE inhibition in humans, cancer development in laboratory animals, reproductive and developmental toxicity in animals, the pharmacokinetics and metabolism of malathion, and immunotoxicological effects. Development of more sensitive biological monitoring methods would be helpful in confirming dose estimates.

DHS recognizes that considerable data are already available for the assessment of health risks of malathion, and that these data may be adequate to support the continued registration for use in agriculture to control insect pests. However, DHS also recognizes that data are developed for a pesticide to evaluate its use in applications in agricultural settings are not necessarily the same data that would be required for public health reasons to assure that the periodic application of the same pesticide over a large human population would be safe. Such an evaluation for the assurance of public safety for pesticide application into urban areas would require a more extensive database, given the added requirements that need to be met to assure the protection of diverse and potentially more susceptible urban populations.

Because of the concerns set forth in this document, specifically the small margins of safety for

certain groups in the population, and the need to develop additional information suitable for evaluating exposures of urban populations to malathion, DHS recommends that the aerial application of malathion-bait in urban areas to eradicate agricultural pests be reconsidered. DHS recognizes the public concerns related to the urban aerial application of pesticides such as malathion to control economic pests, and urges the development and use of more selective pest control methods that are less potentially toxic, intrusive, and alarming.